

Appendix L: Investigational New Drugs (IND)

An **investigational drug** is a drug that is under study in humans, but does not yet have permission from the U.S. Food and Drug Administration (**FDA**) to be legally marketed and sold in the United States. These FDA regulatory requirements also apply to medical care provided to military and civilian DoD healthcare beneficiaries OCONUS. Investigational drugs are either: **1)** entirely new drugs, vaccines, or therapeutics which have never been licensed by the FDA for ANY human use; or, **2)** drugs, vaccines, blood products, or therapeutics which are currently licensed for specific indications, but not for the purpose for which you intend to use them.

Examples

- The USAMRIID tularemia LVS vaccine has not been licensed by the FDA, and thus its use is investigational.
- Anthrax Vaccine Adsorbed (AVA) is licensed for PREexposure prevention of anthrax in adults. It would be considered investigational when used for POSTexposure prophylaxis of anthrax, or for use in children.

A drug that has been approved by the FDA for ANY indication may be prescribed by an individual physician for “off-label” use on a case-by-case basis. For example, cidofovir is licensed for treating cytomegalovirus retinitis in HIV patients, but not for the treating generalized *Vaccinia*. A physician could decide to prescribe cidofovir for an individual case of generalized *Vaccinia*. In that situation, the physician assumes the legal risk as would occur with any medical intervention. But because this is not an FDA-licensed indication for the drug, it cannot legally be official policy (e.g., of the hospital, the DoD, etc.) to treat all cases of generalized *Vaccinia* with cidofovir.

The Drug Licensure Process: if a drug, vaccine, or other therapeutic appears promising from rigorous testing in animals for treating or preventing a specific human disease, a **sponsor** may apply for FDA approval to study the drug in people. This is called an **Investigational New Drug (IND) Application**. Once the IND is approved, clinical trials may begin. **Clinical trials** are research studies designed to determine the safety and effectiveness of the drug in people. Once clinical trials are completed, the sponsor submits the study results in a **New Drug Application (NDA)** or **Biologics License Application (BLA)** to the FDA. This application is carefully reviewed and, if the drug is found to be reasonably safe and effective, it is approved. This whole process can take years to a decade or longer. One of the major historical hurdles for licensing products to treat or prevent diseases caused by the “classic” BW agents is demonstrating effectiveness of the measure in the natural setting. Because these diseases occur in humans rarely, it is impossible to test the effectiveness and it is unethical to challenge humans with potentially deadly disease just to test a new drug. Fortunately, the FDA recently enacted the animal rule, which will allow a new drug to be licensed for BW diseases if it meets strict criteria for effectiveness in acceptable animal models.

The IND Process: the IND process involves an agreement between the sponsor and the FDA to use the product in question in rigidly defined conditions and with very close administrative supervision defined by a research protocol that has been approved by a human ethical and scientific review board and the FDA. The sponsor for all DoD IND protocols is the U.S. Army Surgeon General, whose representative is the U.S. Army Medical Materiel Development Activity (USAMMDA). The Centers for Disease Control and Prevention (CDC) sponsors BW-related INDs for U.S. civilians. IND products must be administered only by specifically trained **investigators**, who must have received **Good Clinical Practices (GCP)** training, are familiar with the investigational protocol, and have signed an **FDA form 1572** (a legally binding “contract” with the FDA to follow the IND protocol “to the letter”). All recipients of the product (**subjects**) must meet specific eligibility criteria and acknowledge having received informed consent with their signature before receiving the product. Therefore, participation in the protocol is voluntary and cannot be required or coerced. This informed consent requirement can only be released by a presidential waiver, under very special and limited circumstances. A mandatory requirement for the investigational use of a product is documentation of the administration of the product, with strict accountability of product shipment, storage conditions, and for any doses that were given. All use of an IND product requires monitoring for adverse events, or **AE**, after product use.

Instructions for Receipt and Administration of Investigational Drugs for Military Healthcare Providers

1. **Call USAMRIID.** Military healthcare providers should call USAMRIID to discuss the case with the medical officer on call, who is familiar with the protocols for administration of the IND products (1-888-USA-RIID during duty hours or DSN: 343-2257 or commercial 301-619-2257 during non-duty hours to reach the 24-hour security desk at USAMRIID). If the use of the investigational product is indicated, USAMRIID will coordinate with USAMMDA for shipping the product.
2. **Determine who will administer the product and where.** There are several options.
 - a. Designate an investigator for the IND at the requesting site. The proposed investigator must meet eligibility criteria (GCP training, signed FDA form 1572 and copy of protocol, etc...) and be approved by the sponsor. This can be arranged through USAMMDA.
 - b. DoD has pre-trained, designated investigators who are already established at several of the major MEDCENs who could potentially travel to the patient to administer the IND product. Alternatively, the patient could be evacuated to the nearest medical center with a pre-trained, designated investigator who will administer the product.
 - c. The U.S. Army has previously designated certain qualified individuals to serve on a Special Medical Augmentation Team (SMART-IND) to administer IND products. For large numbers of casualties, or the need for a time-critical IND administration,

USAMMDA might consider sending a SMART-IND team to run the protocol and administer the IND product.

Instructions for Receipt and Administration of Investigational Drugs for Civilian Healthcare Providers

1. Civilian healthcare providers should first contact their **state health departments** for guidance.
2. If further consultation is required
 - a. For smallpox or smallpox vaccine AE related products, call **CDC Clinical Information Line (CIL)** at 1-877-554-4625.
 - b. For botulinum antitoxin, state health departments should call 770-488-7100. The call will be taken by the **CDC Emergency Operations Center**, which will page the Foodborne and Diarrheal Diseases Branch medical officer on call.
 - c. For other questions, consider calling the **CDC Drug and Immunobiologics Service** (404-639-3670).